REMARKS

I. Support for the Amendments

This application is a continuation of Application Serial No. 07/902,500. The above revisions of the specification simply duplicate corrections of typographical, grammatical, and punctuation errors that were made in the parent application. Also, in Table 1, on page 9, certain decimal numbers have been revised to conform to U.S. practice.

The claims have been rewritten and expanded in number. In the parent application, claims to the method of treating hypertriglyceridemia were allowed, but claims to the composition were rejected, as were claims to a method of treating hypertension and a method of treating "multiple risk factors for cardiovascular diseases." The rejected claims were cancelled in the parent application, in order to allow the claims for the treatment of hypertriglyceridemia to proceed to issuance without delay. By this amendment, the rejected and cancelled claims of the parent application are presented again for examination. Applicants submit that the claims find adequate support in the application as originally filed, for the same reasons as were given when submitting the claims in the parent application, which reasons are repeated in the following paragraphs:

Regarding Claim 16, support for the recitation of a method for elevating the HDL cholesterol level in the serum

of a human patient may be found on page 4, at line 21, of the specification.

Regarding Claims 17, 30, 43, 54, and 92, the inclusion of at least 85% by weight of long chain omega-3 fatty acids is found in the disclosure at page 5, 6th line from the bottom, through page 6, line 2 of the specification, as well as in original Claim 5.

Regarding Claims 18, 31, 44, 55, and 66, the use of 40 to 60 weight percent of EPA (C 20:5 omega-3) is disclosed at page 8 of the specification, in Table 1, as is the use of 25 to 45 weight percent of DHA (C 22:6 omega-3).

Regarding Claims 19, 32, 45, 60, 61, 62, 72, 73, 74, 84, 90, and 93, the use of an EPA:DHA weight ratio of from 1:1 to 2:1 is disclosed at page 5, line 4 of the specification.

Regarding Claims 20, 46, 90, 91, and 92, the inclusion of at least 4.5 weight percent of fatty acids other than EPA and DHA that have 20-22 carbon atoms is supported by original Claim 5.

Regarding Claims 21, 33, 47, 63, and 82, support for the limitation that at least 3 weight percent of the composition is comprised of omega-3 fatty acids other than EPA and DHA that have 20-22 carbon atoms is found at page 6, lines 3-5 of the specification.

Regarding Claims 22, 35, 48, 53, and 67, the presence of at least 1% by weight of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid (C 21:5 omega-3) is supported by the disclosure at page 8 of the specification, in Table 1. The presence of 1 to 4% of that fatty acid (Claims 58 and 70) is also disclosed in Table 1.

Regarding Claims 23, 36, 49, 76, 95, and 99, use of the acids in esterified form is disclosed, for example, at page 5, last paragraph, of the specification.

Regarding Claims 24, 37, 50, 77, 96, and 100, use of the acids in ethyl ester form is disclosed, for example, at page 5, lines 11-14; page 6, lines 11-16; and page 19, lines 4-5 of the specification.

Regarding Claims 25, 51, 78, and 101, use of the fatty acids in salt form is disclosed, for example, at page 4, lines 12-14, and page 5, lines 11-14 of the specification.

Regarding Claims 26, 38, 52, 82, and 102, use of the fatty acids in the free acid form is disclosed, for example, at page 5, lines 11-14, and page 6, third full paragraph of the specification.

Regarding Claims 28, 40, 75 and 98, the use of an oral dosage form of the composition is disclosed at several places in the specification, including page 18, lines 4-5.

Regarding Claim 29, support for the recitation of a method for the treatment or prophylaxis of hypertension may

likewise be found at page 4, second full paragraph, of the specification.

Regarding Claims 41 and 42, support for this method-of-treatment claim (addressing multiple risk factors for cardiovascular diseases) is found, among other places, at page 17, third and fourth paragraphs, and page 18, first full paragraph, of the specification.

Regarding Claims 56 and 68, the inclusion of at least 1 weight percent of C 20:4 omega-6 fatty acid also is disclosed in Table 1 on page 8.

Regarding Claims 57 and 69, the inclusion of at least 1 weight percent of C 22:5 omega-3 fatty acid likewise is disclosed in Table 1, on page 8 of the specification.

Regarding Claims 59 and 71, the inclusion of 1 to 3 weight percent of C 22:5 omega-3 fatty acid likewise is disclosed in Table 1, on page 8 of the specification.

Regarding Claims 64 and 83, recitation of the presence of 3 to 5 weight percent of omega-3 fatty acids other than EPA and DHA that have 20-22 carbon atoms also finds support at page 6, lines 3-5 of the specification.

Regarding Claim 84, support for component (a) may be found in the sentence bridging pages 4 and 5 of the specification for this application. Support for the recitation of component (b) may be found in the sentence bridging pages 5 and 6. Support for component (c) appears in the first full paragraph on page 6. Support for component

(d) (the fatty acid C 21:5 omega-3) may be found in Table 1, on page 8 of the specification.

Regarding Claim 86, support may be found in the sentence bridging pages 4 and 5 of the specification.

Regarding Claim 87, support for the recitation of the presence of tocopherol may be found in the last paragraph on page 18 of the specification.

Regarding Claim 97, support for the recitation that the fatty acids are present in the form of an alkyl ester can be found in Claim 9 of the application as originally filed.

II. The Reasons Why the Present Claims Are Patentable

A. Claims 16-28: Method of Elevating HDL Cholesterol

The allowed claims in Applicants' parent application are all directed to a method of treating hypertriglyceridemia. Claims 16-28 of this application are substantially identical to those allowed claims, except that they call for the fatty acid mixture to be administered for the purpose of "elevating the HDL cholesterol level in the serum of a human patient." Data as to the effectiveness of the claimed method for this purpose are found in the Rule 132 Declaration of Dr. Tone Schanche, dated October 7, 1993, which was filed in the parent application on October 26, 1993. A copy of that declaration is enclosed. Exhibits 6, 7, and 8 show the effects of administering three different fatty acid mixtures: one containing only 62.5 wt.% EPA+DHA (Exh. 6), one using an 80 wt.% EPA+DHA mixture (Exh. 7), and

one using an 85 wt.% EPA+DHA mixture (Exh. 8). Applicants' claims require the use of at least about an 80 wt.% EPA+DHA mixture. In the clinical studies reported by Dr. Schanche, a larger percentage of the subjects in the 80 wt.% and 85 wt.% test groups had their HDL cholesterol raised than in the 62.5 wt.% test group.

As further evidence of the efficacy of the method of Claims 16-28 for raising HDL cholesterol levels, Applicants submit herewith a copy of a 1994 report by Eritsland and Armesan on a study conducted on coronary artery bypass patients, entitled "The Effect of Omacor™ in Patients with Hypertriglyceridemia Having Undergone Coronary Artery Bypass Grafting." The drug, referred to as Omacor, was a fatty acid ester mixture as recited in Claims 16-28. It contained a combined amount of EPA+DHA of approximately 85 wt. %, in an EPA:DHA ratio or about 1.5:1. As regards the HDL aspect of the study, it was a one-year trial, conducted on 198 patients whose serum triglyceride concentrations were greater than 2 mmol/l. A statistically significant increase in HDL cholesterol was found in the Omacor group after 6 and 9 months (p. 9, Table 4). If the Examiner would like this report to be substantiated by a Declaration Under Rule 132, Applicants will be happy to oblige.

In rejecting claims in Applicants' parent application, the Examiner seemed to rely most on two references: U.S. 3,158,541 to *Sutherland* and U.S. 5,130,061

to *Cornieri et al.* However, none of the claims in Applicants' parent application was directed to a "method of elevating the HDL cholesterol level in the serum of a human patient." Applicants submit that neither *Sutherland* nor *Cornieri et al.* anticipates or renders obvious these new method-of-treatment claims. *Sutherland* appears to speak only of "lowering blood cholesterol" (col. 2, l. 30) and makes no mention of raising HDL cholesterol. *Sutherland* advises: "All of the natural polyunsaturated fatty acids, of 20 or more carbon atoms, are practically equally effective." (Column 3, lines 28-30.) One example is given, using a mixture of 17 different fatty acids, containing a combined weight of EPA+DHA of only 62.5 wt.%. Thus, as compared to Applicants' Claims 16-28, *Sutherland* fails to appreciate the importance of using a mixture containing at least 80 wt.% EPA+DHA and makes no mention at all of using such a mixture to raise HDL cholesterol levels.

Cornieri et al. describe a process for the preparation of a mixture of fish oil fatty acid alkyl esters that is enriched in EPA and DHA content. The patentees suggest using the mixture for "the prophylaxis of diseases related to platelet hyperaggregation conditions, since it is completely free from linolenic acid derivatives which are precursors of arachidonic acid. . . ." (Column 4, lines 3-12.) The mixture is described as having a total EPA+DHA content of "at least about 65%." (Column 2, lines 31-34.)

However, the percentage referred to is as determined by gas chromatography (col. 4, l. 34-36), which means that the *weight* percent of EPA and DHA in the mixture is far less than 65. This will be discussed in more detail later in these remarks. For purposes of Claims 16-28, however, suffice it to say that there appears to be no suggestion in *Cornieri et al.* of any method of raising one's HDL cholesterol level, let alone a method that uses a fatty acid mixture containing 80 *weight* percent or more of EPA+DHA.

Accordingly, allowance of Claims 16-28 is believed to be in order and is respectfully requested.

B. Claims 29-40: Method for Treating Hypertension

Claims 29-40 are the same as the allowed claims in Applicants' parent application, except that they are directed to a method for the treatment or prophylaxis of hypertension. Applicants' clinical data showing their fatty acid mixture's hypotensive effect on both systolic and diastolic blood pressure are discussed in the portion of their specification running from page 11, line 12, through page 14, line 5.

It appears that neither *Sutherland* nor *Cornieri et al.* suggests using their compositions to lower blood pressure. Accordingly, it is submitted that this set of claims also is in condition for allowance.

C. Claims 41-102: Method and Composition for Treatment of Multiple Risk Factors for Cardiovascular Diseases

Claims 41-52 are directed to that aspect of Applicants' invention that concerns the treatment or prophylaxis of multiple risk factors for cardiovascular diseases. Claims 53-102 are directed to the fatty acid composition per se, and they describe it in claims of varying scope, setting forth different preferences with respect to the ingredients.

In Applicants' parent application, the corresponding claims to Nos. 41-102 herein were finally rejected on grounds of anticipation by, as well as obviousness in view of, *Cornieri et al.* Applicants responded to the final rejection with a Request for Reconsideration, a copy of which is enclosed herewith. In arguing for withdrawal of the rejection, Applicants contended (1) that *Cornieri's* effective publication date for its disclosure of fatty acid mixtures having an EPA+DHA content above 69% was not until after Applicants' priority date, (2) that even the full text of *Cornieri et al.* does not enable one to make fatty acid mixtures having an EPA+DHA *weight* percent that is any higher than about 46.5, and (3) that Applicants were submitting Rule 131 Declarations to swear behind even the *parent* filing date of *Cornieri et al.*

By an Advisory Action dated July 17, 1995 (copy enclosed), the Examiner replied that Applicants' arguments

and Rule 131 Declarations had been considered, but were not found persuasive. However, the Examiner added, the claims directed to the method of treating hypertriglyceridemia, upon further consideration, were deemed allowable. The Advisory Action included a list of reasons for adhering to the final rejection of the other claims (which are Nos. 41-102 of this application). Having not yet responded to those reasons, Applicants will do so now.

The Examiner's first reason was as follows:

> "1. The affidavit presented under Rule 131 does not overcome the reference because said affidavit does not show a completion of the invention. Evidence commensurate with the scope of the claims to show completion is required. See MPEP 715.03." (Emphasis by the Examiner.)

Copies of the Rule 131 Declarations are enclosed, to complete the file of this case. The *Cornieri et al.* parent filing date was May 26, 1988. Applicants' priority application was filed in the United Kingdom less than three months later, on August 11, 1988. The purpose of the Rule 131 Declarations was to show (a) introduction into the United States of the conception of Applicants' invention prior to May 26, 1988, (b) that that introduction was followed by diligent work in the U.S. toward an actual reduction to practice, and (3) that that work continued up until Applicants' *constructive* reduction to practice, that is, their filing of their British priority application. See Staehelin v. Secher, 25 USPQ2d 1513, 1521 (PTO Bd. App. & Int. 1992) (conception was adequately proved where samples of

claimed substance were received in U.S., together with written characterization of the nature of the samples) and In re Mulder, 219 USPQ 189 (Fed. Cir. 1983) (effort toward reduction to practice sufficient if continued until filing date of foreign priority application). The enclosed declarations describe how a supply of Applicants' preferred composition, containing approximately 85 wt.% of EPA+DHA, was sent by them to the U.S. prior to May 26, 1988, and how their U.S. collaborators then analyzed and used the drug to conduct a clinical study that was still ongoing when the British priority application was filed.

In response to the first sentence in the above-quoted Reason No. 1 of the Advisory Action, Applicants are not required to show a completion of their invention before the *Cornieri et al.* filing date. They are only required to show conception coupled with reasonable diligence to reduce the invention to practice, continued up until their priority application filing date. In re Mulder, supra.

Citing MPEP 715.03, the Examiner contended in Reason No. 1 that Applicants' Rule 131 Declarations were also inadequate because they did not show work in the U.S. commensurate with the scope of the claims.

First of all, Paragraph 715.03 of the MPEP is not relevant. It deals with a situation in which the applicant in a chemical case is presenting generic claims that have been rejected on a reference that discloses one species

within the genus. The MPEP says that the applicant has two ways of antedating the reference: either show that he or she was in possession of the generic invention prior to the effective date of the reference, or show possession of the same species prior to the reference. In the present situation we are not dealing with a genus/species relationship, and MPEP 715.03 is simply not relevant.

Secondly, when the issue is a Section 102 or 103 rejection, and not a priority contest, it is not required that an applicant show a reduction to practice that is commensurate with the scope of the claims. It is sufficient to merely show that applicant did everything done by the author of the publication, prior to the publication date. In re Wilkinson and Boothe, 134 USPQ 171 (CCPA 1962).

The Examiner's second reason for adhering to the rejection over *Cornieri et al.* was as follows:

> "2. The effective date of *Cornieri* is at least May 24, 1989. Applicants priority document is dated August 11, 1988, but does not comply with 35 USC 112 with regard to the instantly claimed subject matter. See In re Gosteli 10 USPQ 2d 1614 Kawai v. Metlesics 178 USPQ 158." (Emphasis by the Examiner.)

In re Gosteli states that a patent applicant may antedate prior art by relying on the benefit of a previously filed foreign application, provided the foreign application supports the U.S. claims in the manner required by 35 U.S.C. § 112. Based upon a telephone conversation between Applicants' undersigned counsel and the Examiner, Applicants

understand that the Examiner was contending in Reason No. 2 that there is not adequate support in Applicants' priority application for the instantly claimed limitation that "at least 80% by weight of the total fatty acid content of the composition is comprised of a combination of [EPA+DHA]" (Claims 41-89), or that "the combined weight of the EPA and DHA constitutes at least 85% by weight of the total fatty acids" (Claim 90), or that "the combined weight of the EPA and DHA constitutes at least 90% by weight of the total fatty acid" (Claim 91).

There are a number of differences between the disclosures in Applicants' priority application and the present application, but the two have a common thread. Both disclose the use of a fatty acid mixture rich in EPA and DHA, but also containing minor amounts of three other C_{20-22} fatty acids, to treat hypertension. The U.K. application gives one specific example (Table 1) of the composition to be used. It has the following characteristics:

Total fatty acids:	99 wt.%
Total C_{20-22} omega-3 fatty acids:	90.1 wt.%
EPA (*C 20:5 omega-3*):	54 wt.%
DHA (*C 22:6 omega-3*):	32.6 wt.%
EPA/DHA (wt. ratio):	1.65/1
EPA+DHA:	86.6 wt.%
Other C_{20-22} fatty acids:	4.9 wt.%
Other C_{20-22} omega-3 fatty acids:	3.5 wt.%
(All-Z omega-3)-6, 9,12,15,18-heneicosapentaenoic acid (*C 21:5 omega-3*):	1.5 wt.%
C 20:4 omega-6 fatty acid:	1.4 wt.%
C 22:5 omega-3 fatty acid:	2 wt.%

The above example is repeated in the present specification, at page 8. In the U.K. application it is said to be useful for treating hypertension. In the present application it is said to be useful not only for treating hypertension, but also for treating multiple risk factors for cardiovascular diseases -- namely, mild hypertension, hypertriglyceridemia, high LDL cholesterol, low HDL cholesterol, and high coagulation factor VII phospholipid complex activity.

With regard to present Claims 90 and 91, it seems indisputable that they are both supported by Applicants' priority application. Claim 90 calls for a composition containing at least 85% by weight of EPA+DHA. The above example shows precisely 86.6 wt.% of EPA+DHA, which is

tantamount to saying "at least 85%." See Ex parte Jackson, 110 USPQ 561 (P.O. Bd. App. 1956).

As for Claim 91, it calls for at least 90% by weight of EPA+DHA. The same "90%" figure appears in the U.K. application, which states, "The total amount of the long chain omega-3 acids will be at least 75% by weight, preferably at least 90% by weight, more preferably at least 95% by weight *with EPA+DHA content being at least 90% by weight*." (Page 5, lines 9-13.) Reason No. 2 is therefore clearly not applicable to either Claim 90 or Claim 91.

The rest of Applicants' claims call for a lower amount of EPA+DHA -- namely, at least 80 wt.%. The suggestion in the Examiner's rejection is that Applicants' U.K. specification describes lower and higher minimums -- 70% and 90% -- but not an 80% minimum. (See page 4, lines 4-13, and page 5, lines 6-13, of the U.K. specification.) But the court instructs in In re Gosteli that the priority application "does not have to describe exactly the subject matter claimed. . . the description must clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." 10 USPQ 2d at 1618. Applicants submit that the disclosure in their U.K. specification of "at least 70%," with a specific example of 86.6% and a stated preference for "at least 90%," clearly allows a person of ordinary skill in the art to recognize that Applicants invented what is now claimed, the use of "at

least 80%" EPA+DHA. See, for example, McLaughlin v. Roberts, 197 USPQ 831, 835 (PTO Bd. Pat. Int. 1978) (where application discloses 10 to 79% of an ingredient, "preferably 40 to 79% thereof and more preferably 40 to 60%," one of ordinary skill in the art would consider that use of later-claimed 10 to 25% range would be part of applicant's invention).

The third and last reason given in the July 17 Advisory Action for maintaining the rejection of claims corresponding to present Claims 41-102 was as follows:

> "3. It is clear that the scope of the evidence must be commensurate with what is being claimed as well as the prior art which evidence has not been presented. See In re Susi: 169 USPQ 42." (Emphasis by the Examiner.)

In re Susi (169 USPQ 423) concerns a situation in which the rejected claims were directed to a small group of chemical compounds, and the prior art described in general terms a much larger group of compounds that encompassed the small group. The reference cited examples of some of the contemplated compounds in the large group, but none of those was a compound falling within the applicant's small group. Although not an anticipation, this broad prior art teaching made it proper for the Examiner to reject the claim to the small group of compounds on the basis of prima facie obviousness. In reply, the Applicant contended that he had made an inventive selection because his small group of compounds surprisingly performed better than the large group

as a whole. However, he presented no performance data for any of the compounds specifically disclosed in the prior art reference. Because of that, the court found that he had not *proved* better performance with respect to the compounds specifically named in the prior art, and therefore had not overcome the prima facie showing of obviousness.

Unlike the situation in In re Susi, Applicants in this case have presented performance data for the closest composition disclosed in the prior art -- namely, the fatty acid mixture in *Sutherland* that contained 62.5 wt.% EPA+DHA. The implication of the July 17 Advisory Action, however, is that *Cornieri et al.* discloses something closer to Applicants' composition and method. Applicants respectfully disagree.

Whereas Applicants are claiming weight percent, *Cornieri et al.* refer only to "[p]ercentages of the fatty acids. . . determined by G.C." (Column 4, lines 34-36.) Cornieri et al. took care to put an asterisk beside the percent sign in their list of ingredients reported in column 4 at lines 37-47. That is like putting the percent sign in quotation marks. It means that what is reported is not the true weight percent of EPA and DHA in the patentees' mixture; it is something called the "gas chromatography area percent." The corresponding "weight percent" number would be much lower, because the gas chromatography area percent relates only to a part of the composition, to wit, the fraction that

passes through the chromatographic column. As explained by an independent expert in marine oil analysis who studied the *Cornieri et al.* disclosure at Applicants' request, that patent's GC area percent has to be divided by approximately 1.5 to convert it to weight percent. Thus, for example, a *Cornieri et al.* GC area percent reading of 69, after being divided by 1.5, equals 46 weight percent. (See enclosed copy of the Declaration by Jeanne M. Joseph, filed in Applicants' parent application.)

Nor is there any suggestion in *Cornieri et al.* of a way to arrive at Applicants' composition. Example 1 of the patent describes how to obtain a mixture containing an EPA:DHA ratio of 4:3. There is no attempt by *Cornieri et al.* to describe how to make a mixture that is enriched beyond Example 1's 69.7% EPA+DHA (GC basis) and still keep the EPA:DHA ratio within Applicants' claimed range of 1:2 to 2:1, let alone keep the ratio within Applicants' *preferred* range of 1:1 to 2:1. What *Cornieri et al.* disclose how to make from the initial EPA+DHA mixture is a product "having a DHA ethyl ester content greater than 95%." (Column 3, lines 45-49.) That represents an EPA/DHA ratio of at least about 24. This is a teaching away from the EPA:DHA ratio recited in Applicants' claims, which, at maximum, is only 2.

Applicants have described, through the work and words of experts from three different institutions, how it is simply not possible, by following the teaching in *Cornieri et*

al., to obtain an omega-3 fatty acid mixture containing more than about 46.5 weight percent of EPA+DHA. Enclosed for ease of reference are copies of the declarations of Dr. Harald Breivik, Prof. Robert G. Ackman, and Ms. Jeanne D. Joseph, in which this fact, with supporting test data, is explained in detail. Such an unrefuted showing, *explaining*, not challenging, the disclosure in a U.S. patent, should be considered by the PTO as "highly probative." In re Payne, 203 USPQ 245 (CCPA 1979).

III. Request for an Interview

Applicants respectfully request that they be given the opportunity to have an interview with the Examiner in charge of this application, in order to discuss in more detail the scientific basis for their assertion that the disclosure in *Cornieri et al.* is limited to fatty acid mixtures containing far less EPA and DHA than Applicants require in the present invention. Applicants sincerely believe that such an interview would facilitate the examination process, if conducted before the first Examiner's Action, and they ask the Examiner to please call the undersigned attorney to schedule such an interview. Applicants' attorney can be reached by telephone at (202) 347-8100.

All written communications for Applicants in this application should continue to be sent to the address below.

Copies are enclosed of all of the court opinions cited in the above discussion.

Respectfully submitted,

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